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(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING A BISPHOSPHONATE AND THEIR USE FOR NASAL ADMINISTRATION

(57) Abstract

Pharmaceutical compositions containing a bisphosphonate or a salt thereof, optionally together with an enhancer for nasal absorption, and their use for nasal administration. The enhancer for the nasal absorption preferably is sodium tauro-24,25-dihydrofusidate (STDF).

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Pharmaceutical compositions containing a bisphosphonate and their use for nasal administration

The present invention relates to new pharmaceutical compositions containing a bisphosphonate and their use for the nasal administration to patients suffering from diseases where treatment with a bisphosphonate is indicated.

Bisphosphonates (or diphosphonates) are drugs which can be used in certain diseases involving calcium metabolism, such as Paget's disease, hypercalcaemia due to malignancy, osteoporosis and rheumatoid arthritis.

Bisphosphonates have hitherto been administered either orally or intravenously to patients. However, the oral absorption is poor and often accompanied by gastro-intestinal side effects. Furthermore, the degree of absorption shows substantial individual variations. Consequently, intravenous administration has up till now had to be used whenever a rapid and reliable delivery of bisphosphonates was needed.

Thus, there is a need for a suitable way of administering bisphosphonates enterally, but despite the fact that this problem has existed for more than a decade, no solution has been found.

It has now surprisingly turned out that in spite of their very polar nature it is possible to administer bisphosphonates through the nasal route, thereby not only avoiding the side effects encountered with oral administration, but even obtaining a degree of absorption which is several times higher than that obtained after oral administration.

It has further turned out that the addition of penetration enhancers to the pharmaceutical preparation

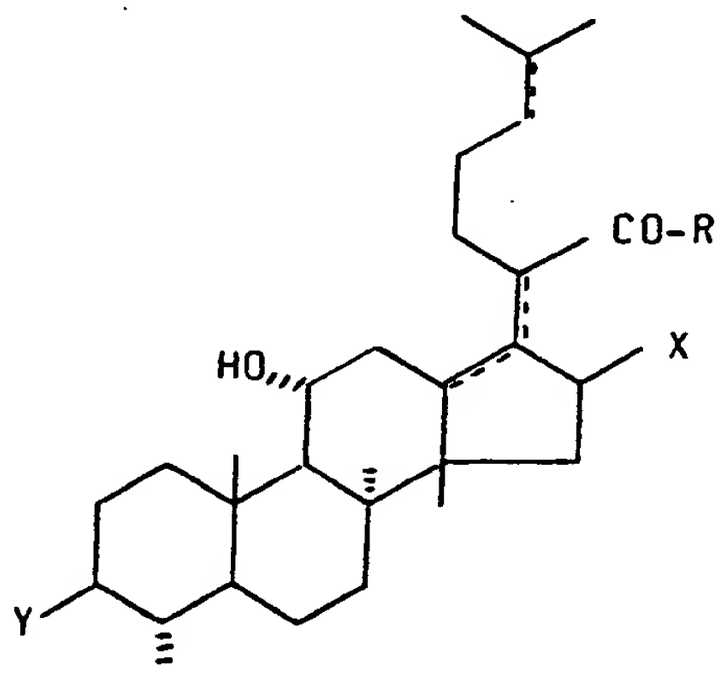
intended for nasal administration improves the absorption of some bisphosphonates dramatically. It is known (European patent application, publication No. 128831) that penetration enhancers can be used to improve the nasal absorption of compounds of higher molecular weight, such as insulin, glucagon and calcitonin, but it was not to be expected that such enhancers would be able to improve the absorption of compounds of relatively low molecular weight like bisphosphonates.

Any bisphosphonic acid or salt thereof suitable for treatment of patients can form part of the pharmaceutical compositions according to the present invention. As examples of such bisphosphonic acids, mention may be made of

1-hydroxy-alkylidene-1,1-bisphosphonic acids, e.g.
1-hydroxy-ethylidene-1,1-bisphosphonic acid (etidronate) or
1-hydroxy-pentylidene-1,1-bisphosphonic acid;
dichloromethylene-bisphosphonic acid (clodronate);
difluoromethylene-bisphosphonic acid;
3-amino-1-hydroxy-propylidene-1,1-bisphophonic acid (APD);
3-(N,N-dimethylamino)-1-hydroxy-propylidene-1,1-bis-phosphonic acid;
3-(N,N-diethylamino)-1-hydroxy-propylidene-1,1-bisphosphonic acid;
4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid;
4-(N,N-dimethylamino)-1-hydroxy-butylidene-1,1-bisphosphonic acid;
5-amino-1-hydroxy-pentylidene-1,1-bisphosphonic acid;
6-amino-1-hydroxy-hexylidene-1,1-bisphosphonic acid;,
2-(2'-pyridyl)-ethylidene-1,1-bisphosphonic acid;
N-(3'-methyl-2'-pyridyl)-aminomethylenebisphosphonic acid;
(4-chlorophenylthiomethylene)-bisphophonic acid (SR 41319);
compounds described and claimed in international patent application PCT/DK85/00071 filed on July 25, 1985 (claiming priority from British patent application No. 8419489, filed on July 31, 1984); and compounds described and claimed in international patent application PCT/DK86/00132 filed on December 10, 1986 (claiming priority from British patent application No. 8530603, filed on December 12, 1985).

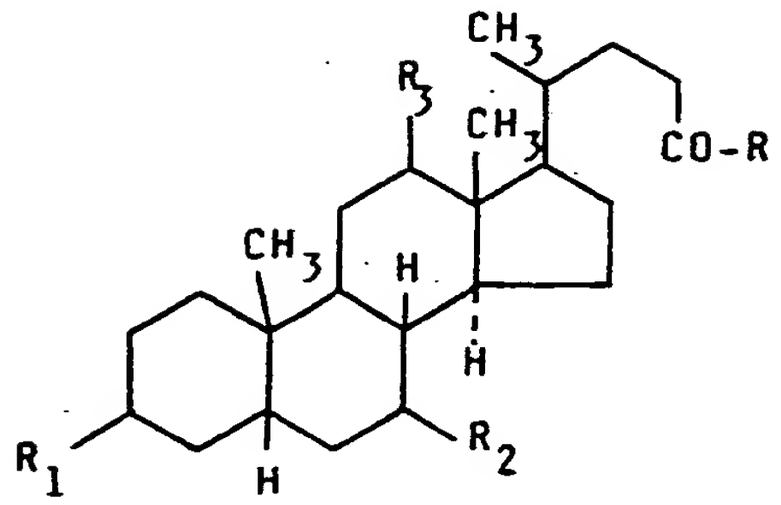
The bisphosphonic acids are tetrabasic acids which can form mono-, di-, tri- and tetra-salts with bases. In the compositions of the present invention, the bisphosphonic acids are preferably being used in the form of neutral salts with pharmaceutically acceptable bases.

Examples of suitable enhancers for the nasal absorption of bisphosphonates include, but are not limited to, compounds of the general formula I:



(I)

in which X (in the α- or β-position) stands for hydrogen, OH-, -O-alkyl, -O-acyl, -S-alkyl, -S-acyl or halogen; Y (in the α- or β-position) stands for -OH, -O-alkyl, -O-acyl, halogen, -O-alkylsulfonyl, -O-arylsulfonyl; R stands for -OH or -NHZ, and in which the dotted lines indicate the possibility of double bond(s); when R represents -NHZ, then Z stands for alkyl or aryl, substituted with carboxyl, sulfonic acid groups, and/or quaternary ammonium groups; or compounds of the general formula II:



(II)

wherein R_1, R_2, and R_3 (in the α- or β-position), which can be the same or different, each stands for hydrogen or -OH, and in which R has the same meaning as in formula I, provided that not all R_1, R_2, R_3 can be hydrogen at the same time. The compounds of formula I and II are preferably used in the form of pharmaceutically acceptable salts.

The pharmaceutical composition of the present invention is formed into a nasal preparation.

In the nasal preparation, the physiologically active bisphosphonate is contained as the drug, optionally together with an absorption enhancer.

The nasal preparation according to the present invention can be produced by conventional processes. For example, small amounts of a pH adjusting agent, preservative, thickening agent (natural gums, cellulose derivatives, acrylic acid polymers, vinyl polymers etc.) and/or excipients are incorporated.

The nasal preparation of the present invention may take a solid, liquid or semi-liquid form. In the case of a solid form, the above components may be simply blended or be freeze-dried to provide a powdery composition, the preferred particle size in either case being about 20 to 250μ. In the case of a liquid preparation, it is preferably an aqueous solution, an aqueous suspension or an oil suspension. The semi-solid preparation is preferably an aqueous or oleaginous gel or ointment.

As to the proportion of each component in the nasal preparation, the content of bisphosphonate in the final preparation is about 0.005 to 50 w/v% and preferably about 0.01 to 30 w/v% and the optional content of absorption enhancer is from 0 to 5 w/v%, preferably from 0 to 1 w/v%.

In the case of a liquid or semi-liquid preparation, the amount of bisphosphonate in the preparation is about 0.001 to 50 w/v% and preferably about 0.05 to 40 w/v%, and the optional content of absorption enhancer is from 0 to 5 w/v%, preferably from 0 to 1 w/v%.

The excipient is exemplified by glucose, mannitol, inositol, sucrose, lactose, fructose, starch, corn starch, microcrystalline cellulose, hydroxypropylcellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, etc.

The liquid preparation can be produced by known procedure. For example, an aqueous preparation for nasal administration can be produced by dissolving, suspending or emulsifying the active components in water, a buffer solution or an aqueous medium. The oil suspension for nasal use can be produced by suspending or emulsifying the active components in an oleaginous base.

The above mentioned oleaginous basis is examplified by various oils and fats such as sesame oil, olive oil, corn oil, soybean oil, cotton seed oil, peanut oil, lanoline, vaseline, paraffin, coparaffinate, silicone oil, glycerol fatty acid having 6 to 30 carbon atoms or its glycerol ester or its alcoholic ester, or a mixture thereof.

As to the semi-solid preparation, an aqueous or oleaginous gel or ointment can be produced by the per se conventional procedure. For example, such an aqueous gel for nasal administration can be produced in the following manner. First, an aqueous solution or suspension of the active components is prepared and, if required, a pH adjusting agent, a preservative and/or the like are added. The solution is divided into halves and an aqueous gel base is dissolved or dispersed in one of the halves and heated or cooled to give a stable gel. The two halves are combined and evenly mixed to give an aqueous gel preparation.

Adjustment of the pH of the preparation can be effected by adding an acid, a base, a buffer solution or the like in the course of the production of the preparation. As examples of the acid, there may be mentioned inorganic acids (like hydrochloric acid, boric acid, phosphoric acid, carbonic acid, etc), amino acids and organic acids (e.g. monocarboxylic acids, oxycarboxylic acids, polycarboxylic acids). The base is exemplified by sodium hydroxide, potassium hydroxide, sodium hydrogen carbonate, sodium carbonate etc.

Examples of the aqueous gel basis include natural gums (e.g. gum tragacanth, gum acasia, gum karaya, Irish moss, gum guaiac, gum xanthane, locust bean gum etc), cellulose derivatives (e.g. methylcellulose, carboxymethylcellulose etc), acrylic acid polymers (e.g. polyacrylic acid, polymethacrylic acid etc), vinyl polymers (e.g. polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl methyl ether, carboxypolymethylene etc), synthetic polysaccharides (e.g. polysucrose, polyglucose, polylactose etc), starch, dextrin, pectin, sodium alginate etc. These bases may be used in the form of appropriate mixtures of two or more species.

The oleaginous ointment for nasal administration can be produced by dispersing the active components evenly in a hot melt of an oleaginous base and cooling the same under stirring. The oleaginous base may be one of those mentioned hereinbefore.

Preservatives may be incorporated in nasal preparations. Examples of such preservatives include phenolic compounds such as phenol, cresol etc; alcohols such as chlorobutanol, phenylethyl alcohol, propylene glycol etc; invert soaps such as benzalkonium chloride, benzethonium chloride etc; benzoic acid, sorbic acid, dehydroacetic acid and sulfurous acid and salts thereof; acids and their salts such as sodium hydrogen sulfite.

If the nasal preparation of the invention is in solid form, it can be administered in the following exemplary way. A capsule containing the powdery preparation is set in an exclusive dust applicator equipped with needles to pierce

the capsule at the top and bottom thereof and an air balloon is used to drive the powdery contents into the nasal cavity.

In the case of a liquid preparation, it is put into a nasal douche, an atomizer or a spray-mist applicator suited for nasal application of liquids and dripped or sprayed into the nasal cavity.

The semi-solid preparation can be administered, for example by filling a tube with the preparation and sending the preparation directly into the nasal cavity through an applicator attached to the mouth of the tube or by administering the indicated dose of the preparation by means of a nasal insertion device.

While the dosage of the bisphosphonate varies with its kind, the disease to be treated, and the patient to be treated, the proper amount of the solid preparation per dose is about 5 mg to 100 mg, that of the liquid preparation is about 0.05 to 0.5 ml, and that of the semi-solid preparation is about 50 mg to 500 mg. The nasal preparation may be administered from one to about four times per day.

The invention also relates to a method for treating patients suffering from a disease where treatment with a bisphosphonate is indicated, such as Paget's disease, hypercalcaemia due to malignancy, osteoporosis and rheumatoid arthritis, said treatment consisting of administering to the patient in need of treatment an effective amount of the present composition.

The following Examples shall illustrate the invention, but not limit its scope.

Example 1

Nasal absorption of (phenoxymethylene)-bisphosphonic acid (EB 899) in dogs

Preparation I:

Disodium (phenoxymethylene)-bisphosphonate:	7.50 g
Water:	60 ml
Ethanol:	10 ml
2N NaOH:	to pH = 7.6

The final solution was diluted with water to a total volume of 100 ml.

Preparation II:

Preparation I containing 1 w/v% sodium tauro-24,25-dihydrofusidate (a compound of formula I)

Experiments

Preparation II was sprayed into the nasal cavity of 2 dogs. Preparation I was given either orally, intravenously or nasally (as a spray) to the same two dogs. Urine (0 - 24 hours) was collected in all four experiments and the urinary excretion of EB 899 was determined analytically.

Dog No.	Route of administration	Preparation	Dose of EB 899-di-Na (mg)	Amount excreted mg	% of theory
521	nasal	II	115.8	51.3	44.3
523	nasal	II	123.8	36.2	29.3
521	nasal	I	120.1	9.6	8.0
523	nasal	I	123.8	10.2	8.2
521	i.v.	I	12.1	7.8	64.5
523	i.v.	I	11.7	7.1	60.7
521	oral	I	130.1	2.2	1.7

Example 2

The following preparation may be used for the nasal administration of the disodium salt of 3-amino-1-hydroxy-propylidene-1,1-bisphosphonic acid (APD) either as drops or as a spray:

Disodium salt of APD	5.0 g
Sodium tauro-24,25-dihydrofusidate	0.5 g
Water, to a total volume of	100 ml

Example 3

For the nasal administration of 3-(N,N-dimethylamino)--1-hydroxy-propylidene-1,1-bisphosphonic acid, the following preparation may be used:

Disodium 3-(N,N-dimethylamino)-1-hydroxy--propylidene-1,1-bisphosphonate	0.5 g
Water, to total volume of	100 ml

Example 4

Nasal absorption of 3-amino-1-hydroxy-propylidene-1,1-bisphosphonic acid-1-^{14}C (^{14}C-APD) in dogs

In order to test the nasal absorption of 3-amino-1-hydroxy-propylidene-1,1-bisphosphonic acid, the following preparations were prepared:

Preparation I:

3-Amino-1-hydroxy-propylidene--1,1-bisphosphonic acid-1-^{14}C	150 mg
Saturated aqueous $NaHCO_3$ to make a solution with pH = 7.5	
Water to make a total volume of	3 ml

Preparation II:

As preparation I but with 15 mg (0.5% w/v) sodium tauro-24,25-dihydrofusidate added.

Three anaesthetized beagle dogs were treated with preparation I either intranasally (as drops) or intravenously. Preparation II was only given intranasally (as drops). Blood samples were drawn at 7, 15, 30, 45 and 60 minutes and at 2, 3, 4, 6 and 24 hours after drug administration. The blood levels of ^{14}C-APD (pg/ml) were determined by measuring the radioactivity in the blood samples. AUC (area under blood concentration curve) values were calculated, and the nasal absorption was estimated by comparing AUC-values after nasal and intravenous

administration.

Dog No.	Route of administration	Preparation	Dose of ^{14}C-APD	AUC (h x pg/ml)
219	nasal	I	30 mg	2484
413	nasal	I	30 mg	2728
514	nasal	I	30 mg	2044
103	nasal	II	30 mg	2660
213	nasal	II	30 mg	3766
229	nasal	II	30 mg	2888
103	i.v.	I	30 mg	16068
213	i.v.	I	30 mg	11992
229	i.v.	I	30 mg	15930

Example 5

Nasal absorption of (4-thiomorpholinylmethylene)bis-phosphonic acid (^{14}C labelled) in dogs

The following preparations were made:

Preparation I

(4-Thiomorpholinylmethylene)-bisphosphonic acid (^{14}C-labelled) SL 2261-^{14}C 150 mg

Saturated aqueous $NaHCO_3$ to make a solution with pH = 7.5

Water to a total volume of 3 ml

Preparation II

As preparation I, but with 15 mg (0.5% w/v) sodium tauro-24,25-dihydrofusidate added.

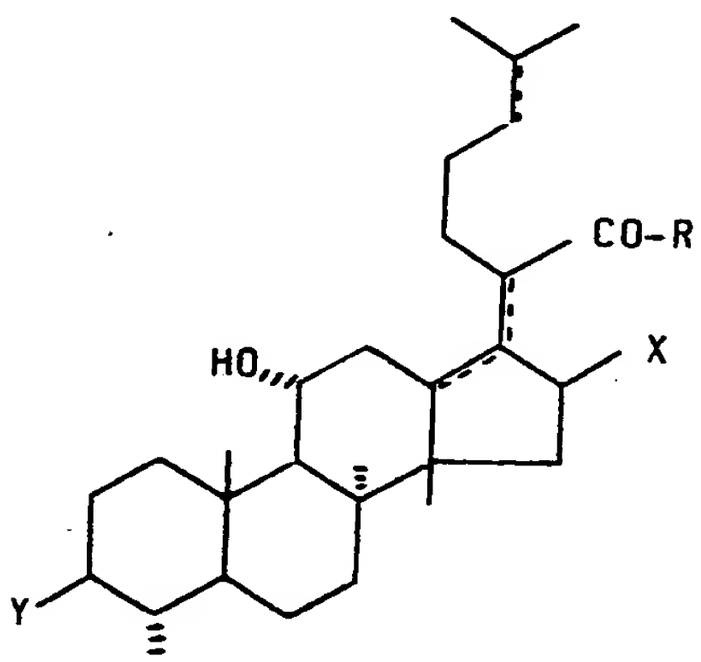
Absorption studies were carried out in 3 beagle dogs as described in Example 4.

Dog No.	Route of administration	Preparation	Dose of SL 2261-^{14}C	AUC h x pg/ml
219	nasal	I	30 mg	3280
413	nasal	I	30 mg	5306
514	nasal	I	30 mg	8398
219	nasal	II	30 mg	4686
413	nasal	II	30 mg	3058
514	nasal	II	30 mg	8288
219	i.v.	I	30 mg	8782
413	i.v.	I	30 mg	9362
514	i.v.	I	30 mg	13518

WHAT WE CLAIM IS:

1. A composition for the administration of a bisphosphonate to patients in need of treatment, comprising as an active ingredient a bisphosphonate or a salt thereof, together with pharmaceutically acceptable, non-toxic carrier(s) and/or auxiliary agent(s), said compositions being used for nasal administration.

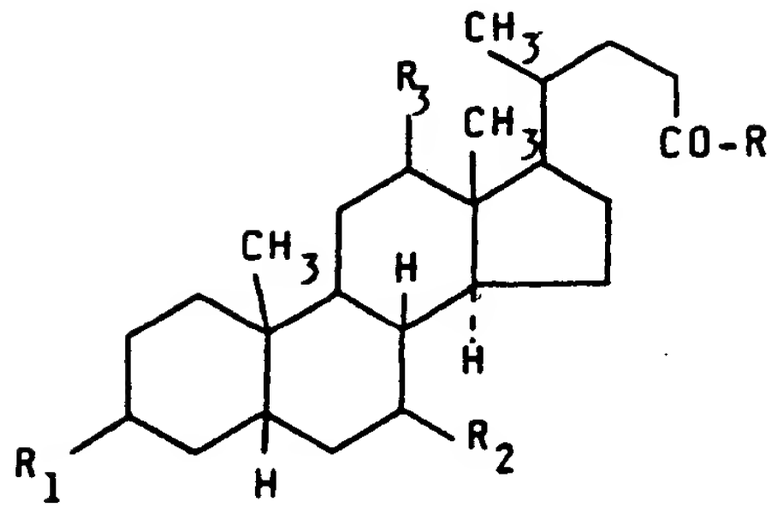
2. A composition according to claim 1, which in addition to the bisphosphonate or a salt thereof contains as an enhancer for the nasal absorption, a compound of the formula I:



(I)

in which X (in the α- or β-position) stands for hydrogen, -OH, -O-alkyl, -O-acyl, -S-alkyl, -S-acyl or halogen; Y (in the α- or β-position) stands for -OH, -O-alkyl, -O-acyl, halogen, -O-alkylsulfonyl, or -O-arylsulfonyl; R stands for -OH or -NHZ, Z being alkyl or aryl, substituted with carboxyl, sulfonic acid groups, and/or quaternary ammonium groups; and in which the dotted lines indicate the possibility of double bond(s);

or a compound of the formula II:



(II)

wherein R_1, R_2, and R_3 (in the α- or β-position), which can be the same or different, each stands for hydrogen or -OH, and in which R has the above meanings, provided that not all R_1, R_2, and R_3 can be hydrogen at the same time; or a pharmaceutically acceptable salt of such compound of formula I or II.

3. A composition according to claim 1 or 2, in which the bisphosphonate is a member selected from the group consisting of
1-hydroxy-ethylidene-1,1-bisphosphonic acid;
1-hydroxy-pentylidene-1,1-bisphosphonic acid;
dichloromethylene-bisphosphonic acid;
difluoromethylene-bisphosphonic acid;
3-amino-1-hydroxy-propylidene-1,1-bisphosphonic acid;
3-(N,N-dimethylamino)-1-hydroxy-propylidene-1,1-bisphosphonic acid;
3-(N,N-diethylamino)-1-hydroxy-propylidene-1,1-bisphosphonic acid; 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid;
4-(N,N-dimethylamino)-1-hydroxy-butylidene-1,1-bisphosphonic acid; 5-amino-1-hydroxy-pentylidene-1,1-bisphosphonic acid;
6-amino-1-hydroxy-hexylidene-1,1-bisphosphonic acid;,
2-(2'-pyridyl)-ethylidene-1,1-bisphosphonic acid;

N-(3'-methyl-2'-pyridyl)-aminomethylene-bisphosphonic acid;
(4-chlorophenylthiomethylene)-bisphosphonic acid;
(phenoxymethylene)-bisphosphonic acid;
(4-thiomorpholinylmethylene)-bisphosphonic acid;
(+/-)-(3-isobutyl-4-thiomorpholinylmethylene)-bisphosphonic acid;
(+)-(3-isobutyl-4-thiomorpholinylmethylene)-bisphosphonic acid;
(-)-(3-isobutyl-4-thiomorpholinylmethylene)-bisphosphonic acid.

4. A composition according to claim 2, in which the enhancer is sodium tauro-24,25-dihydrofusidate (STDF).

5. A composition according to any one of claims 1-4, in which the bisphosphonate is present in an amount of from 0.005 to 50 (w/v) %, preferably from 0.01 to 30 (w/v) %.

6. A method for the treatment of patients suffering from diseases involving calcium metabolism, such as Paget's disease, hypercalcemia due to malignancy, osteoporosis and rheumatoid arthritis, in which an effective amount of a composition according to any one of claims 1 to 5 is administered to such patients in need of treatment.

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK87/00084

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC 4

A 61 K 31/66

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
IPC 2,3,4	A 61 K 31/66, /665, /67, /675, 9/06, /12, /72, 45/06, /08
IPC 1	A 61 k 27/00, 13/00

.../...

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
A	EP, A2, 0 023 359 (TEIJIN LIMITED) 4 February 1981 See especially page 7, line 29	1
X,Y	EP, A2, 0 128 831 (M C CAREY ET AL) 19 December 1984 See inter alia page 10, line 1 - page 11, line 2, page 17, lines 6-8 and claim 71 & US, 4548922 JP, 61033126	1-5
X	EP, A2, 0 129 285 (THE PROCTER & GAMBLE CO) 27 December 1984 See especially page 8, lines 5-8 and page 29, line 29 - page 30, line 6 & JP, 60036423 US, 4537776 AU, 559095 CA, 1223818	1

.../...

* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1987-10-23	1987 -10- 28
International Searching Authority	**Signature of Authorized Officer**
Swedish Patent Office	Martin Hjälmdahl

LH

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

II Fields searched (cont)

US Cl 424:198, 204, 222;
514:108, 141

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim number 6, because it relates to subject matter not required to be searched by this Authority, namely:

Method for treatment of the human or animal body by therapy [PCT Rule 39 (iv)]

2. [ ] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
P	EP, A2, 0 189 662 (THE PROCTER & GAMBLE CO) 6 August 1986 See page 26, lines 28-32	1
X,Y	GB, A, 2 096 889 (ISTITUTO GENTILI SPA) 27 October 1982 See especially page 5, lines 19-23 & BE, 891891 FR, 2499408 DE, 3201865 NL, 8200298 JP, 57167915 LU, 83931 CA, 1174602 US, 4578376	1-5
X	US, A, 4 067 971 (THE PROCTER & GAMBLE CO) 10 January 1978 See especially column 20, lines 22-24 & JP, 53009324	1
X,Y	US, A, 4 234 645 (THE PROCTER & GAMBLE CO) 18 November 1980 See especially column 2, lines 33-43	1-5